REMARKS

The Claim Amendments

Claim 1 has been amended to recite a chemically modified double stranded siNA molecule comprising a distinct sense strand and an antisense strand. Claim 1 has also been amended to recite an antisense strand that "comprises nucleotide sequence of about 18 to about 27 nucleotides that is complementary to a human huntingtin (HD) nucleotide sequence" and a sense strand that "comprises a portion of said HD sequence of about 18 to about 27 nucleotides". Claim 1 has also been amended to recite the limitation of "about 100% of nucleotide positions in one or both strands of said siNA molecule are chemically modified". Support for the amendment to claim 1 can be found, *inter alia*, at page 8, line 1; page 10, lines 10-15; page 11, lines 12-18; page 11, line 26 to page 12, line 7; and page 13, lines 14-28. Claim 1 and dependent claims 3, 13-21, and 30-31 have been amended to recite the term "siNA" rather than "double stranded nucleic acid". Support for these amendments can be found, *inter alia*, pages 2, 7, 69-72, throughout the specification, and in the claims as originally filed. New claim 32 recites that the chemical modification can be phosphorothioate internucleotide linkage, 2'-O-methyl ribonucleotide, 2'-deoxy-2'-fluoro ribonucleotide, 2'-deoxy ribonucleotide, universal base nucleotide, 5-C-methyl nucleotide, and inverted deoxyabasic modifications. Support for this claim can be found, *inter alia*, at page 13, lines 1-7 and throughout the specification. Claims 10-12 have been canceled with this amendment. Claims 2, 4-9, 22-29, and 32-35 were previously canceled.

Amendments to the claims are made without prejudice and do not constitute amendments to overcome any prior art or other statutory rejections and are fully supported by the specification as filed. Additionally, these amendments are not an admission regarding the patentability of subject matter of the canceled or amended claims and should not be so construed. Applicant reserves the right to pursue the subject matter of the previously filed claims in this or in any other appropriate patent application. The amendments add no new matter and applicants respectfully request their entry.

McDonnell Boehnen Hulbert & Berghoff LLP
300 South Wacker Drive, Suite 3200
Chicago, IL 60606
Tel: (312) 913-0001
Fax: (312) 913-0002

Claim Objections

Claim 30 was objected to because of dependency to a canceled claim (claim 9). Claim 30 has been amended accordingly and is now dependent from claim 1. Applicants respectfully request withdrawal of the objection.

Rejection of claims under 35 U.S.C. § 103 as obvious

Claims 1, 3, 10-14, 19-21 and 31 were rejected under 35 U.S.C. 103(a) as being unpatentable over Hayden *et al.* in view of Agrawal *et al.* in further view of Bennett *et al.* Claims 10-12 have been canceled, thus rendering the rejection moot with respect to these claims. Applicants respectfully traverse the rejection with respect to claims 1, 3, 13-14, and 31.

The Applicants submit that the Office Action has not established a *prima facie* case of obviousness with respect to the presently amended claims. Claim 1 has been amended to recite a chemically modified double stranded short interfering nucleic acid (siNA) molecule comprising a distinct sense strand and an antisense strand. Claim 1 has also been amended to recite an antisense strand that "comprises nucleotide sequence of about 18 to about 27 nucleotides that is complementary to a human huntingtin (HD) nucleotide sequence" and a sense strand that "comprises a portion of said HD sequence of about 18 to about 27 nucleotides". Claim 1 has also been amended to recite the limitation of "about 100% of nucleotide positions in one or both strands of said siNA molecule are chemically modified". In the present case, the combination of the references fails to teach or suggest the claimed siNA molecules having all of these features.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the references, when combined must teach or suggest all the claim limitations. *See* MPEP §2143.

Hayden *et al.* teach a single stranded antisense molecule targeted to an HD gene. Agrawal *et al.* teach or suggest a single stranded self-stabilized antisense molecule. Bennet *et al.* teach single stranded antisense molecules that contain certain chemical modifications. None of these references, alone or in combination, teach or suggest an siNA molecule, much less "a chemically modified double stranded short interfering nucleic acid (siNA) molecule comprising a distinct sense strand and an antisense strand". Furthermore, none of the cited references, either alone or in combination, teach an siNA comprising a structure where the antisense strand "comprises nucleotide sequence of about 18 to about 27 nucleotides that is complementary to a human huntingtin (HD) nucleotide sequence", and the sense strand "comprises a portion of said HD sequence of about 18 to about 27 nucleotides".

The Office states that Agrawal teaches a double-stranded antisense having self-stabilizing regions and argues that it would have been obvious to incorporate the double-stranded self-stabilizing regions taught by Agrawal into the single-stranded antisense compound targeted to HD taught by Hayden and further obvious to incorporate the chemical modifications taught by Bennet. The Office also states that there would have been a reasonable expectation of success because Hayden teaches antisense targeted to HD and Agrawal teaches that self-stabilized antisense are more resistant to degradation and hyper stabilized by chemical modifications, and Bennet teaches that chemical modifications stabilize antisense molecules.

Applicants respectfully submit that there are several flaws with this argument. First, as discussed above, none of the cited references teach or disclose the structure of an siNA molecule, much less an siNA molecule targeted to HD. Contrary to the Office's implication, the structure of an siNA molecule is NOT obvious from the teachings of antisense molecules. Further, the cited references, even in combination, do not teach or render obvious the specific elements of the claimed siNA molecule. That is, they do not teach an siNA comprising a distinct sense strand and an antisense strand where the antisense strand comprises nucleotide sequence of about 18 to about 27 nucleotides that is complementary to a human huntingtin (HD) nucleotide sequence and the sense strand

comprises a portion of said HD sequence of about 18 to about 27 nucleotides. In the absence of any teaching whatsoever relating to siNA technology, one skilled in the art would have no motivation to make such molecule and further would have no reasonable expectation that such molecule could successfully be made.

Furthermore, as discussed in further detail below, one would not have had a reasonable expectation that the chemical modifications discussed for antisense molecules would have been applicable to siNA molecules with any kind of success. The claimed siNA molecules require that about 100% of nucleotide positions in one or both strands of said siNA molecule are chemically modified. Neither Agrawal nor Bennet suggests that the antisense molecule can have about 100% modified nucleotides. Thus, one skilled in the art would not have been motivated to make or achieve reasonable success with such a modified siNA.

The cited references, alone or in combination, do not teach or suggest all the claim limitations and therefore the combination of Hayden *et al.* Agrawal *et al.* and Bennett *et al.* cannot render the instantly claimed invention obvious. Accordingly, Applicant respectfully requests withdrawal of the 35 U.S.C. § 103(a) rejections based on these teachings.

Claims 1, 3, 10-21, 30 and 31 stand rejected under 35 U.S.C. 103(a) as being obvious over Hayden *et al.*, Hammond *et al.*, Tuschl *et al.* (WO 02/44321), Parrish *et al.*, and in further view of Matulic-Adamic *et al.*, Thomson *et al.*, and Schmidt *et al.* Claims 10-12 have been canceled, thus rendering the rejection moot as applied to these claims. Applicants respectfully traverse the rejection as it applies to amended claims 1, 3, 13-21, 30 and 31.

The Applicants submit that the Office has not established a *prima facie* case of obviousness with respect to the presently claimed invention. In the present case, there is no suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine reference teachings to arrive at the presently claimed invention. As described

below, Applicants submit that the cited art, especially the teachings of Tuschl *et al.* teach away from the presently claimed invention. If the prior art references teach away from the claimed invention, there can be no motivation to combine the references to arrive at the claimed invention, as is the case here. *In re Grasselli*, 713 F.2d 731, 743, 218 USPQ 769, 779 (Fed. Cir. 1983).

The Office action asserts that it would have been obvious to one of ordinary skill in the art at the time the invention was made to make a double stranded nucleic acid molecule as taught by Hammond *et al.*, Tuschl *et al.*, and Parrish *et al.*, to target a gene encoding HD, as taught by Hayden *et al.* Further, the Office action asserts that it would have been obvious for one of ordinary skill in the art to make a double stranded nucleic acid molecule with chemical modifications, as taught by Tuschl *et al.*, Parrish *et al.*, and Matulic-Adamic *et al.*

However, in contrast to the Office's assertions, there would have been no motivation to combine the teachings of Hayden with the teachings of Hammond as the Office suggests. The Office argues that the motivation to use a double stranded nucleic acid targeted to HD instead of an antisense is found in Hayden *et al.*, which teaches that using dsRNA to inhibit gene expression is more sequence specific than using antisense methodologies and RNAi using dsRNA is a more potent method requiring only a few molecules of dsRNA per cell. (Office Action, page 9). However, Hammond merely teaches a generalized approach to RNAi and fails to even consider HD as a potential target for RNAi. In the absence of any mention whatsoever of HD as a target for RNAi, there is no suggestion or motivation to combine the teachings of Hayden with those of Hammond.

Current case law mandates that there must be a *specific* suggestion to combine the particular references to arrive at the claimed invention.

> When patentability turns on the question of obviousness, the search for and analysis of the prior art includes evidence relevant to the finding of whether there is a teaching, motivation, or suggestion to select and combine the references relied on as evidence of obviousness. The factual

> inquiry whether to combine references must be thorough and searching. It must be based on objective evidence of record. This precedent has been reinforced in myriad decisions, and cannot be dispensed with. *The need for specificity pervades this authority.*

In re Lee, 61 USPQ2d 1430, 1434 (Fed. Cir. 2002) (emphasis added); *see also In re Deuel*, 34 U.S.P.Q.2d 1210, 1215 (Fed. Cir. 1995) (the prior art must suggest the particular form of the invention and how to make it; general guidance is insufficient); and *In re Obukowicz*, 27 U.S.P.Q.2d, 1063, 1065 (Bd. Pat. App. Int. 1992) (Prior art "that gives only general guidance and is not at all specific as to the particular form of the claimed invention and how to achieve it . . . does not make the invention obvious").

In the absence of a specific and identifiable suggestion to make the particular combination of Hammond with Hayden, all that remains is that it would have been obvious to try siRNA against HD because Hammond teaches the benefits of RNAi and Hayden identifies HD as a target. But "obvious to try" is an improper standard for establishing obviousness. (see *In re O'Farrell*, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988).

The Office additionally alleges that one would have been motivated to use a double stranded nucleic acid targeted to HD instead of antisense because it was well known at the time the invention was made that dsRNA molecules are efficient molecules to target and decrease expression of a target gene. (Office Action, page 9). However, at the time the invention was made, the use of siRNA mediated RNAi was in its infancy. Accordingly, the level of skill in the art at the time of the invention was low. Again, at best, it may have been obvious to try siRNA against HD based on the recent introduction of RNAi technology, but "obvious to try" is an improper standard for establishing obviousness.

Although Applicants maintain that the Office has not established a *prima facie* case of obviousness, in the interest of expediting prosecution, Applicant has amended claim 1 to recite *short interfering nucleic acid (siNA)* molecules and require that the siNA molecule comprises *about 100% modification of nucleotide positions in one or both*

strands of said siRNA molecules targeting HD. The non-obviousness of this degree of modification is discussed below in light of the teachings of Tuschl, who attempted to use extensive modification of one or both strands of siRNA without success, thereby effectively teaching away from use of such extensive modification in an siNA molecule.

The Office alleges that Tuschl *et al.*, Parrish *et al.*, and Matulic-Adamic *et al.* together provide motivation to incorporate various chemical modifications. With respect to Tuschl *et al.*, the Applicants submit that Tuschl *et al.* teaches away from the presently claimed invention. In all cases where Tuschl *et al.* attempted extensive modification of one or both strands of siRNA molecules, such modifications were *inactive* (see Figure 14, and discussion on page 46). In fact, the only *active* chemically modified siRNA molecule taught by Tuschl *et al.* is a siRNA having up to four 2'-deoxynucleotides on either strand by substitutions at the four 3'-terminal nucleotides of each strand of the siRNA. No other chemical modification taught by Tuschl *et al.* results in a siRNA that is active to mediate RNAi.

None of the other references, alone, or in combination, are able to rectify the deficiencies of Tuschl *et al.* in teaching away from the presently claimed invention. Tuschl *et al.* is the only reference addressing chemically modified siRNAs having one or both strands with about 100% modification, and all the evidence it provides demonstrates that such siRNAs are inactive. None of the other references relied upon for chemical modifications relate to siRNA. Hayden *et al.* teaches selective modification of antisense nucleic acids that are distinct from the presently claimed siNA molecules. Further, nowhere does it teach or suggest that about 100% of the antisense nucleotides can be modified. Likewise, Matulic-Adamic *et al.*, Thomson *et al.*, and Schmidt *et al.* only teach selective modification of ribozyme nucleic acids that are distinct from the presently claimed siNA molecules. Parrish, while teaching dsRNA as short as 26-bp, only chemically modified long dsRNA constructs of greater than 720 nucleotides in length, and such modification was not even close to about 100% modification. Further, nowhere does it teach or suggest that about 100% of the nucleotides can be modified. Accordingly, the ordinary artisan would have derived no level of assurance from Hayden

et al., Matulic-Adamic *et al.*, Thomson *et al.*, and Schmidt *et al.* that similar modifications in about 100% of the nucleotides would result in active siRNA molecules, particularly when Tuschl *et al.* teaches that about 100% modification of one or both strands of siRNA molecules abolishes RNAi activity.

Importantly, one of skill in the art would not have had any reasonable expectation of success based on the teachings of Tuschl *et al.* (alone or in combination with the other cited references) in targeting HD with siNA molecules that contain about 100% modification of nucleotide positions in one or both strands of the siNA molecule as is presently claimed. As discussed above, Tuschl *et al.* attempted to apply 100% chemical modification to one or both strands of siRNA molecules without success. In fact, in testing siRNA duplexes having modifications (2'-deoxy and 2'-O-methyl), Tuschl *et al.* concludes that "Complete substitution of one or both siRNA strands by 2'-deoxy residues, however, abolished RNAi, as did complete substitution by 2'-O-methyl residues" (see Figure 14 and discussion on page 46). Tuschl *et al.* also states that "More extensive 2'-deoxy or 2'-O-methyl modifications reduce the ability of siRNAs to mediate RNAi, probably by interfering with protein association for siRNP assembly" (Tuschl *et al.*, "*The siRNA Users Guide*", page 49-50 of WO 02/44321).

For the reasons set forth above, one of skill in the art would not have been motivated to make an siNA molecule having about 100% modification of one or both strands of the siNA molecule targeting a human HD sequence as is presently claimed; nor would one of skill in the art have had any reasonable expectation of success with such modified siNA molecule. Therefore, Hayden *et al.*, Hammond *et al.*, Tuschl *et al.* (WO 02/44321), Parrish *et al.*, Matulic-Adamic *et al.*, Thomson *et al.*, and Schmidt *et al.*, alone or in combination, do not render the present claims obvious. Accordingly, Applicant respectfully requests withdrawal of the 35 U.S.C. § 103(a) rejections based on these teachings.

Conclusion

In view of the foregoing amendments and remarks, the applicant submits that the claims are in condition for allowance, which is respectfully solicited. If the examiner believes a teleconference will advance prosecution, she is encouraged to contact the undersigned as indicated below.

Respectfully submitted,
McDonnell Boehnen Hulbert & Berghoff LLP

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By: _____
Anita J. Terpstra
Reg. No. 47,132

McDonnell Boehnen Hulbert & Berghoff LLP
300 South Wacker Drive, Suite 3200
Chicago, IL 60606
Tel: (312) 913-0001
Fax: (312) 913-0002